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(54) ORAL PHARMACEUTICAL PULSED RELEASE DOSAGE FORM

ORALE PHARMAZEUTISCHE DOSIERUNGSFORM BERUHEND AUF STOSSWEISER FREISETZUNG

FORME DE DOSAGE PHARMACEUTIQUE ET ORALE DIFFUSEE PAR IMPULSIONS

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(73) Proprietor: **AstraZeneca AB**
151 85 Södertälje (SE)

(72) Inventors:
- **LUNDBERG, Per, Johan**
  S-431 83 Mölndal (SE)
- **SJÖBLOM, Brita**
  S-431 83 Mölndal (SE)

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WO-A1-96/01623
WO-A1-97/02020
US-A- 5 229 131

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Description

Field of the invention

[0001] The present invention is related to new oral pharmaceutical dosage forms which comprise a proton pump inhibitor, i.e. a H^+,K^+-ATPase inhibitor. The new dosage forms are enteric coated formulations which provide a discontinuous pattern of two or more discrete release pulses of the H^+,K^+-ATPase inhibitor in the small and/or large intestines. The pulses are separated in time by from 0.5 and up to 12 hours, they are preferably separated by from 0.5 and up to 6 hours, and more preferably from 0.5 and up to 4 hours. Furthermore, the present invention refers to the manufacture of such pulsed delayed release pharmaceutical formulations, and their use in medicine.

Background of the invention and prior art

[0002] Acid labile H^+,K^+-ATPase inhibitors also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Some of these compounds are disclosed in EP-A1-0005129, EP-A1-124495, WO 94/27988, EP-A1-174726, EP-A1-166287 and GB 2163747.

[0003] These pharmaceutical substances are useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrom. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease (GORD). They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these.

[0004] Therapeutic control of gastric acid secretion is fundamental in all these disease, but the degree and duration of acid inhibition required for optimal clinical effect is not fully understood.

[0005] It has been proposed by the Applicant in WO97/48380, (published 24 December, 1997 i.e. after the priority date of the instant application,) that an administration regimen that gives blood plasma levels extending from 2-12 hours (by any of several means) will result in a larger fraction of proton pumps being inhibited. Thus, an extended blood plasma level should result in more effective inhibition of acid secretion resulting in improved efficacy in GORD, more rapid healing of gastric ulcer and improved eradication of *H. Pylori*. The present invention provides pharmaceutically dosage forms which achieve such extended plasma levels by releasing the drug in two or more separate pulses.

[0006] A pharmaceutical dosage form of omeprazole or any other proton pump inhibitor is best protected from contact with acidic gastric juice by an enteric coating layer. In US 4,786,505 and US 4,853,230 such enteric coated preparations are described. These preparations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and then with an enteric coating layer. WO 96/01623 and WO 96/01624 describe tableted dosage forms of omeprazole and other proton pump inhibitors, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces. None of these by the Applicant previously described formulations gave a dissolution of two or more pulses separated in time, i.e. in the meaning pulsed release of the proton pump inhibitor which resulted in an extended blood plasma profile.

[0007] There are different technologies and pharmaceutical formulations described in the prior art which aim at a delayed release of an administered drug. Such pharmaceutical formulations are for instance formulations providing different lag times, constructions based on osmotic differences, slow-eroding/dissolving layers, time controlled explosion systems or any combinations thereof. In the following some of these principles are described.

[0008] Gazzaniga et al (Proceed. 12th Pharm. Int. Techn. Conf., 1993, 1, 400-8.) described tablets which were spray-coated or press-coated with HPMC layers to obtain delayed release preparations of ketoprofen or verapamil. The HPMC layer may also contain an insoluble filler. Gazzaniga et al have also described press-coated tablets containing antipyrine with HPMC layers to obtain delayed release, having an outer enteric coating comprising Eudragit L30D applied thereon. (Proc. Inter. Symp. Control. Rel. Bioact. Mater. 1996, 23, 571-2.)

[0009] EP-A1-0629398 describes a dosage form comprising a drug and an organic acid in a core surrounded by a film that controls the start of release, and further covered by an enteric coating layer. This dosage form is not suitable for substances that are sensitive to acidic degradation as the core comprises an organic acid.

[0010] Osmotic systems are described by Fox ("Colon-Targeted Osmotic System for Oral delivery of Peptides and

Proteins", In; Oral Delivery of Proteins, Peptides and other Biopharmaceutical Agents; Proceedings Technology Management Group, Wakefield, MA, USA, Sept. 1991). A colon release system, OROS-CT, is used to obtain delayed extended release after a lag time. The dosage form had an enteric coating which dissolved in the small intestines, the drug release started after a desired lag time and the release was maintained during some hours.

[0011] EP 0384642 and EP 0384646 (as well as Pharm. J., July 27th, 1991 pp.137-9) introduced the PULSINCAP™ dosage form both for enteric coated system and non-enteric coated system. The system comprises a capsule composed of a water insoluble body and a water soluble cap. The drug formulation was contained within the capsule body and sealed within this region by means of a hydrogel plug.

[0012] Conte et al (Drug Development and Industrial Pharmacy, 1989, vol 15, pp. 2583-96) described a three-layer tablet giving a double pulse system suitable for ibuprofen. The first layer contained a rapidly releasing formulation, and was separated from the layer comprising the second dose by a swellable polymeric barrier layer. The second dose was coated with an impermeable film of ethyl cellulose. This construction releases the drug in an acidic medium.

[0013] A dosage form for diltiazem was described in US 5,567,441 comprising a mixture of one fraction of enteric coated pellets with slow release and another fraction of delayed pulse release membrane coated pellets, the latter fraction of pellets were not enteric coated. Such a dosage form will not be suitable for acidic sensitive drugs such as omeprazole or the like.

[0014] There are two newly published patent applications which propose controlled release formulations comprising a proton pump inhibitor, i.e. in WO 97/02020 a dosage form for pantoprazole in combination with an antibacterial substance is proposed. At least a part of the pantoprazole dose shall be in slow-release form with a continuous release of pantoprazole during time. The preparation has one intermediate layer which will remain intact as a layer and is releasing the dose of pantoprazole continuously so as a pantoprazole plasma level persists as long as possible. WO 97/02021 discusses a very similar dosage form of a reversible proton pump inhibitor in combination with an antibacterial substance.

Detailed description of the drawings

[0015] Figures 1 - 5 show graphs illustrating the dissolution profiles for some of the inventive pharmaceutical formulations prepared in the examples. The graphs show the released amount of substance with respect to time. The amount of released substance is identified by registration of the absorbance at 292 nm in a buffer solution.

Figure 1 shows the dissolution profile for single dose layered pellets prepared in Example 1.
Figure 2 shows the dissolution profile for single dose layered pellets prepared in Example 2.
Figure 3 shows the dissolution profile for single dose layered pellets prepared in Example 3.
Figure 4 shows the dissolution profile for single dose layered tablets prepared in Example 5.
Figure 5 shows the dissolution profile for multiple dose layered tablets prepared in Example 6.

Summary of the invention

[0016] The therapeutic effect of omeprazole and similar substances may be improved by providing an extended plasma profile by once daily administration of a dosage form. The present invention obtains such an extended plasma profile by a pharmaceutical dosage form capable of releasing the drug in discrete pulses separated in time, i.e. a dosage form with a discontinuous release pattern. The present invention provides such dosage forms comprising an acid susceptible H^+K^+-ATPase inhibitor, such as omeprazole or any other proton pump inhibitor. A specific problem is that the pharmaceutical dosage forms suitable for a H^+K^+-ATPase inhibitor must fulfill certain requirement with respect to gastric acid resistance for enteric coated articles specified in the US Pharmacopeia (Edition 23).

[0017] According to one aspect of the invention the extended plasma profile of a proton pump inhibitor is provided by once daily administration of a dosage form which, in the small and/or large intestines (but not in the stomach), releases the proton pump inhibitor in two or more discrete pulses separated in time by from 0.5 up to 12 hours, preferably separated in time by from 0.5 and up to 8 hours, and more preferably by from 0.5 and up to 4 hours.

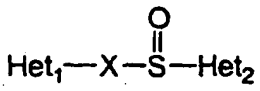
[0018] According to another aspect of the invention a discontinuous release pattern of the proton pump inhibitor by once daily administration of a dosage form is provided wherein a part of the dosage form gives a pulsed delayed release, and other parts of the dosage form release the proton pump inhibitor instantly. The dosage form provides at least two consecutive pulses for release of substance, the pulses should be separated in time by from 0.5 and up to 12 hours, preferably by from 0.5 and up to 8 hours, and more preferably by from 0.5 and up to 4 hours interval.

[0019] The present pulsed release formulations show an improved patient compliance over an administration regimen comprising consecutive administration of two or more unit doses within specified time intervals.

Detailed description of the invention

Active substance.

[0020] Compounds of interest for the novel pharmaceutical formulations according to the present invention are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers



I

wherein

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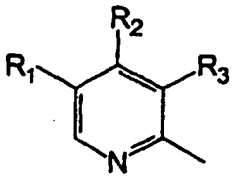

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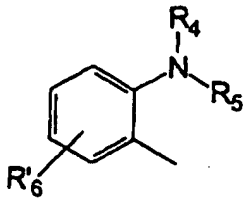

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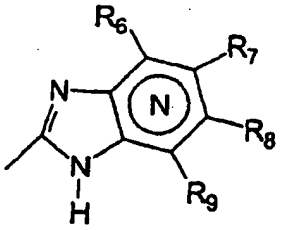

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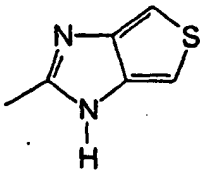

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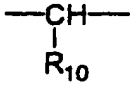

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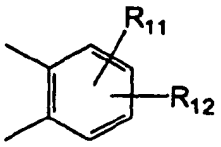


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally maybe-exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and arylalkyl;

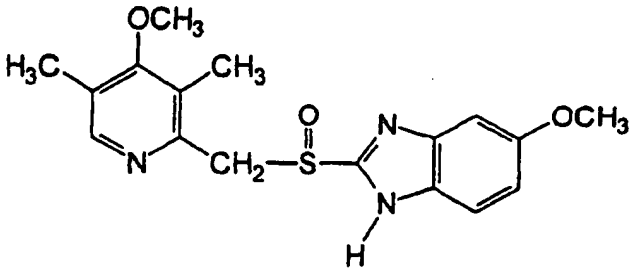
R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolinyl, and trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

Examples of specifically interesting compounds according to formula I are



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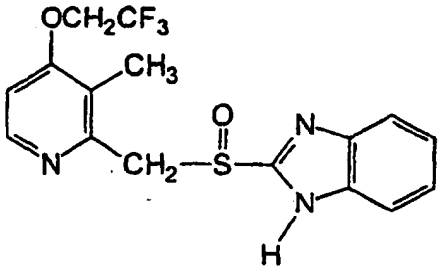
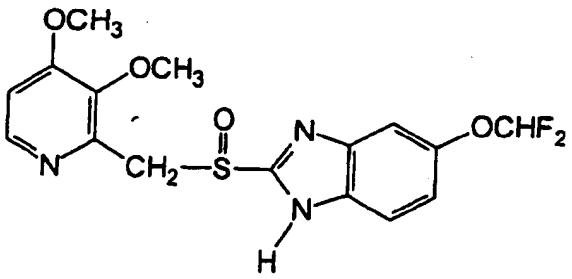
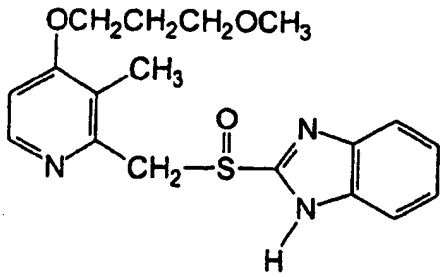
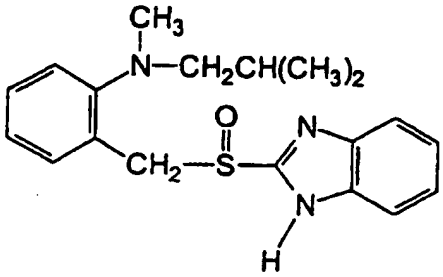
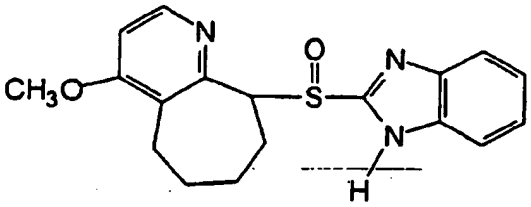
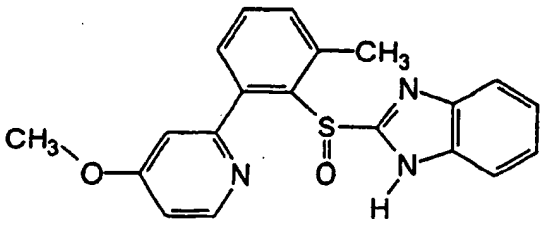


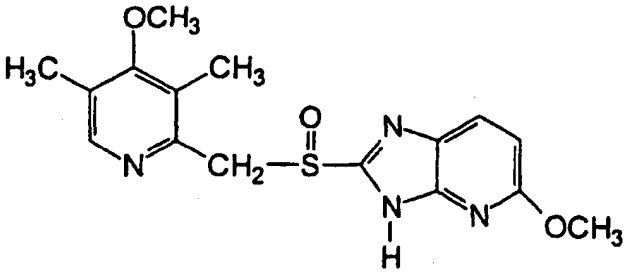


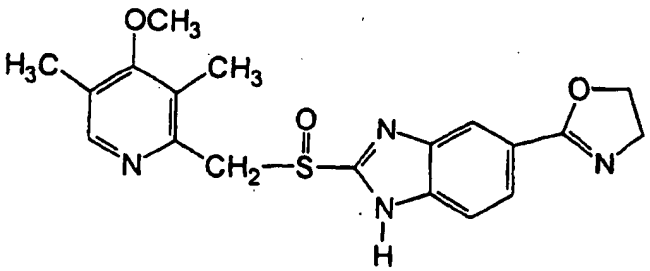












[0021] The compound suitable to be used in the pulsed release formulations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

[0022] Especially preferred compounds for the oral pharmaceutical preparation according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. Omeprazole and related substances as well as their preparations are described in EP 5129, EP 124 495, WO 95/01977, WO 94/27988 hereby incorporated in a whole by references.

[0023] The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230, WO 95/ 01783, and WO 96/ 01623. Especially, the latter describes alternative manufacturing methods for the preparation of enteric coating layered pellets comprising omeprazole and similar compounds.

[0024] The dosage forms according to the invention provide at least a part of the dose with a pulsed delayed release of the drug and another part of the formulation with rapid or instant release. The instant and pulsed delayed release of the drug can be achieved according to different principles, such as

- by single dose layered pellets or tablets,
- by multiple dose layered pellets or tablets, or
- by two or more different fractions of single or multiple dose layered pellets or tablets, optionally in combination with pellets or tablets having instant release.

[0025] Multiple dose layered pellets, or two or more different populations of single or multiple dose layered pellets prepared according to any of the below described principles, are filled into a capsule or together with tablet excipients compressed into a multiple unit tablet. Alternatively, a multiple dose layered tablet may be prepared.

Single dose layered pellets or tablets.

[0026] According to one aspect of the invention, pellets or tablets giving one single delayed release pulse of the drug are prepared. The single dose layered pellets or tablets may be constructed as to comprise the following parts:

- a core material, optionally layered on a seed/sphere, the core material comprises the drug together with a water swellable substance, and optionally pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:
- a surrounding lag time controlling layer, and finally
- an enteric coating layer positioned to cover the lag time controlling layer.

[0027] According to an alternative aspect of the invention, it is also possible to construct the layered pellets or tablets as to comprise the following parts:

- a core material, optionally layered on a seed/sphere, the core material comprises the drug optionally together with pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:

- a surrounding layer comprising a water swellable substance, and thereupon

- a surrounding lag time controlling layer, and finally
- an enteric coating layer positioned to cover the lag time controlling layer.

Multiple dose layered pellets or tablets.

[0028] According to another aspect of the invention, multiple dose layered pellets or tablets giving two or more delayed release pulses of the drug are prepared. These pellets or tablets may be constructed as to comprise the following parts:

- a core material (I), optionally layered on a seed/sphere, the core material comprises the drug together with a water swellable substance, and optionally pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:

- a surrounding lag time controlling layer (II), and
- a layer (III) comprising the drug optionally together with a water swellable substance, and/or pharmaceutically acceptable excipients; the layer is being free from acidic compounds, and
- optionally a separating layer (IV) which is water-soluble or in water rapidly disintegrating,

wherein the layers II and III and the optional layer IV may appear in repeated sequences (in this order) and each set of layers (II + III) gives an additional single pulse of the drug. The dosage form is finally covered by an outer enteric coating layer (V).

[0029] Thus, a three-pulsed delayed release pellet or tablet could be constructed as having the following sequence of layers I+ II + III + II + III + an optional layer IV, and the prescribed outer enteric coating layer (V).

[0030] According to an alternative aspect of the invention, the multiple dose layered pellets or tablets may also be constructed with the following parts:

- a core material (I), optionally layered on a seed/sphere, the core material comprises the drug optionally together with pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:

- a surrounding layer (II) comprising a water swellable substance, followed by
- a surrounding lag time controlling layer (III) and
- a layer (IV) comprising the drug optionally together with pharmaceutically acceptable excipients; the layer is being free from acidic compounds, and
- optionally a separating layer (V) which is water-soluble or in water rapidly disintegrating,

wherein the layers II, III, IV and the optional layer V may appear in repeated sequences (in this order) and each set of layers (II + III+ IV) gives an additional single pulse of the drug. The dosage form is covered by an outer enteric coating layer (VI).

[0031] Thus, a three-pulsed pellet or tablet could be constructed as having the following sequence of layers I+ II + III + IV+ II + III + IV + an optional layer V, and the prescribed outer enteric coating layer (VI).

[0032] The core material comprising the active drug can be prepared either by coating layering the drug onto a seed, such as for instance sugar spheres, or by extrusion-/spheronization of a mixture comprising the drug and pharmaceutical acceptable excipients. It is also possible to prepare the core material by using tablet technology, i.e. compression of drug granules and optionally pharmaceutically acceptable excipients into a tablet core.

[0033] For pellets of the two types, i.e. single or multiple dose pellets, which have the drug deposited onto a seed/sphere by layering, it is also possible to have an optional layer comprising a water swellable substance beneath the drug containing layer in the core material.

[0034] The prepared core material is used for further processing. Different techniques to prepare the core material for pellets or tablets are described below.

Core material

[0035] The core material for the individual pellets or tablets can be constituted according to different principles. A seed/sphere layered with active substance, the active substance is optionally mixed with a water swellable substance and/or a pharmaceutically acceptable excipient, can be used as core material for the further processing. The core material is free from acidic compound except that the active substance as such might be slightly acidic. The micro environment around the acid susceptible H^+K^+-ATPase inhibitor should preferable be not less than pH=7, and more

preferably not less than pH=8 when water is absorbed to the core material mixture or when water is added in small amount to the mixture.

[0036] The seeds/spheres can be water insoluble and comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures, or be water soluble and comprise different inorganic salts, sugars and other materials, alone or in mixtures. Further, the seeds/spheres may comprise active substance in the form of crystals, agglomerates, compacts etc. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

[0037] Before the seeds are layered, the active substance may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture.

[0038] Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, gelatine, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulfate.

[0039] Optionally an osmotic agent is placed in the core material. Such an osmotic agent is water soluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulfate, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium carbonate, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

[0040] Alternatively, the active substance optionally mixed with any of the components defined above can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. For extrusion/spheronization processes incorpaoration of a microcrystalline cellulose and a low-substituted hydroxypropylcellulose in the core material is preferred. The size of the formulated core materials is approximately between 0.1 and 4 mm, preferably between 0.1 and 2 mm for a pellet preparation, and between 2 and 10 mm, preferably between 3 and 7 mm for a tablet preparation.

[0041] Suitable alkaline additives can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.\ 2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids such as arginine, and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

[0042] Alternatively, the aforementioned core material for a pellet preparation can be prepared by using spray drying or congealing techniques.

Swelling layer.

[0043] The applied swelling layer comprises one or more water swellable substances, a suitable binder, and optionally pharmaceutically acceptable excipient(s). Suitable swellable substances, binders, as well as pharmaceutically acceptable excipients are described below. The swelling layer expands when exposed for an aqueous solution such as intestinal fluid.

[0044] Alternatively, one of the additional drug containing layers applied onto the core material may be a combined drug swelling layer.

Water swellable substances.

[0045] Water swellable substances suitable for the dosage forms according to the present invention are compound which are able to expand when they are exposed to an aqueous solution, such as intestinal fluid.

[0046] One or more water swellable substances may be present in the core material together with the active substance and optionally pharmaceutically acceptable excipient(s). Alternatively, one or more water swellable substances are included in a swelling layer applied onto the core material. As a further alternative, swellable substances(s) they may also be present in an optional swelling layer situated beneath the drug containing layer, if a layered seed or sphere is used as the core material.

[0047] The amount and art of water swellable substance(s) in the swelling layer or in the core material is chosen in such a way that the core material or the swelling layer in contact with an aqueous solution, such as intestinal fluid, will expand to such a degree that the surrounding lag-time controlling membrane ruptures. A water swellable substance may also be included in the drug comprising layer of the multiple layered pellets or tablets to increase dissolution rate

of the drug fraction.

[0048] Suitable substances which can be used as water swellable substances are for instance, low-substituted hydroxypropyl cellulose, e.g. L-HPC; cross-linked polyvinyl pyrrolidone (PVP-XL), e.g. Kollidon™ CL and Polyplasdone™ XL; cross-linked sodium carboxymethylcellulose, e.g. Ac-di-sol™, Primellose™; sodium starch glycolate, e.g. Primojel™; sodium carboxymethylcellulose, e.g. Nymcel ZSB 10™; sodium carboxymethyl starch, e.g. Explotab™; ion-exchange resins, e.g. Dowex™ or Amberlite™; microcrystalline cellulose, e.g. Avicel™ ; starches and pregelatinized starch, e.g. Starch 1500™, Sepistab ST200™; and formalin-casein, e.g. Plas-Vita™. One of these substances can be used or any combinations or mixtures thereof, taking into consideration that the use of any acidic compound not is suitable.

Lag time controlling layer.

[0049] The lag time controlling layer is a semipermeable membrane comprising a water resistant polymer that is semipermeable for an aqueous solution, such as intestinal fluid. Suitable polymers are cellulose acetate, ethylcellulose, polyvinyl acetate, cellulose acetate butyrate, cellulose acetate propionate, acrylic acid copolymers, such as Eudragit™ RS or RL. The polymer may optionally comprise pore forming agents, such as a water soluble substance, eg. sucrose, salt; or a water soluble polymer eg. polyethylene glycol. Also pharmaceutically acceptable excipients such as fillers and membrane strength influencing agents such as talc, aerosil, or sodium aluminium silicate may be included.

[0050] There is at least one lag time controlling layer present in the dosage forms according to the invention. The lag time controlling layer positioned nearest the inner core material is constructed in the form of a semipermeable membrane that will disrupt after a desired time after ingestion.

[0051] A desired lag time may be adjusted by the composition and thickness of the layer. The amount of substances forming such a disrupting semipermeable membrane, i.e. a lag time controlling layer, is usually in the range from 0.5 to 25 % counted on the weight of the core material including swelling substances or a swelling layer. Preferably the amount of such a lag time controlling layer, i.e. a disrupting semipermeable membrane , is between 2 to 20 % by weight.

[0052] A preferred disrupting semipermeable membrane, i.e. lag time controlling layer, is composed of a mixture of ethylcellulose and talc. The mixture contains most preferably 10 to 80 % w/w of talc.

[0053] Optionally, any additional lag time controlling layer may be constructed as a disrupting semipermeable membrane.

Enteric coating layer(s) and separating layer(s).

[0054] Before applying an enteric coating layer onto the layered pellets or tablets, they may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including alkaline compounds such as for instance pH-buffering compounds. This separating layer separates the composition of the layered pellets or tablets from the outer enteric coating layer.

[0055] The separating layer as well as the other type of layers, such as the swelling and lag time controlling layers, can be applied by coating or layering procedures in suitable equipments such as coating pan, coating granulator, centrifugal granulator or in a fluidized bed apparatus (including Wurster type) using water and/or organic solvents for the coating process. As an alternative the layer(s) can be applied by using powder coating or press-coating techniques.

[0056] Suitable materials for the optional separating layer are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, pH-buffering substances and other additives may also be included into the separating layer.

[0057] When the optional separating layer is applied to the layered pellets or tablets it may constitute a variable thickness. The maximum thickness of the optional separating layer is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The optional separating layer may improve the chemical stability of the active substance and/or the physical properties of the dosage form.

[0058] Finally the layered pellets or tablets are covered by one or more enteric coating layers by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s).

[0059] Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer. Other compounds

may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. The enteric coating layer(s) constitutes a thickness of approximately at least 10 μm, preferably more than 20 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

[0060] Any of the applied polymer containing layers, and specially the enteric coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

Final dosage form

[0061] The prepared layered pellets, optionally mixed with tablet excipients are filled into a capsule, or compressed into a multiple unit tableted dosage form. Alternatively, the dosage form is a multiple layered tablet. Prepared tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

[0062] The dosage forms according to the invention are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used.

[0063] Preferably, a dosage form of the proton pump inhibitor, for instance 1 - 500 mg is administered once a day. Suitable doses comprise for instance about 5 - 100 mg of the substance, and more preferably 10 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacida.

Examples

[0064] The following examples describe the invention more in detail without restricting it.

Example 1.

[0065] Pulsed single dose delayed release layered pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 44 mg/g).

Preparation of core material (spheres layered with drug).

[0066] A drug containing suspension was made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6 cps	15 g
Polysorbate 80	2 g
Purified water	323 g

[0067] HPMC was dissolved in water during stirring with subsequent addition of Polysorbate 80 and the drug. The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. The weight of the obtained product was 395 g.

Application of a swelling layer

[0068] A (water free) suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g

(continued)

EtOH (99.5%)	3100 g

[0069] HPC-LF was dissolved in ethanol during stirring, then talc and swelling agent L-HPC was added. The suspension was sprayed onto 175 g of the core material from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

Application of lag time controlling layer (semipermeable membrane).

[0070] A coating suspension was made according to the following formula;

Ethylcellulose, 10 cps	10 g
Talc	23 g
EtOH (99.5%)	1000 g

[0071] The ethylcellulose was dissolved in the ethanol during stirring, then talc was added. Spraying of the suspension onto 150 g of swelling layered pellets from above (0.61 - 0.71 mm obtained by sieving) was done in a Wurster equipped fluidized bed. The weight of the obtained pellets was 176 g.

[0072] Pellets (corresponding to approx. 10 mg active substance) were analyzed using USP dissolution apparatus No. 2 (paddle), and operated at 100 rpm, 37°C and with a phosphate buffer pH 6.8. The dissolution of active substance was followed by registration of the absorbance at 292 nm in a buffer solution, using a 0.5 cm flow-through compact cell. The dissolution profile measured at 292 nm is shown in Figure 1.

Example 2.

[0073] Pulsed single dose delayed release layered pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 43 mg/g).

Preparation of core material (spheres layered with drug)

[0074] A drug containing suspension was made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6 cps	15 g
Polysorbate 80	2 g
Purified water	323 g

[0075] HPMC was dissolved in water during stirring with subsequent addition of Polysorbate 80 and the substance. The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. After coating the weight of the obtained product was 395 g.

Application of swelling layer

[0076] A water free suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF(HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

[0077] HPC-LF was dissolved in ethanol during stirring, then talc and swelling agent L-HPC was added. The suspension was sprayed onto 175 g pellets from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

Application of lag time controlling layer (semipermeable membrane).

[0078] 100 g of the swelling layered pellets obtained above were coated to obtain a lag-time controlling layer with the suspension below;

Ethylcellulose, 10 cps	8 g
Talc	9 g
Mg-Stearate	2 g
EtOH (99.5%)	620 g

[0079] The suspension was prepared by dissolving the ethylcellulose in the ethanol during stirring, then the other compounds were added. Spraying of the suspension onto the pellets was done in a Wurster equipped fluidized bed. The weight of the obtained pellets was 116 g.

[0080] The pellets were analyzed as is described in Example 1. The dissolution profile is shown in Figure 2.

Example 3.

[0081] Single dose layered pellets, i.e. enteric coated pulsed single dose delayed release pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 37 mg/g).

Application of enteric coating layer.

[0082] Pellets from Example 1 were enteric coated in a fluidized bed with a coating dispersion according to below;

Eudragit L30 D-55 (30 % w/w dispersion)	73.3g
Triethylcitrate (TEC)	6.6 g
Glycerole monostearate (GMS)	0.3 g
Polysorbate 80	0.03 g
Purified water	40.4 g

[0083] A homogenous coating dispersion was prepared by dispersing polysorbate 80 and glycerol monostearate in water. Triethylcitrate was dissolved in the Eudragit dispersion and thereafter the two dispersions were mixed to obtain the coating dispersion.

[0084] The coating dispersion was applied onto 120 g pellets from Example 1, using a Wurster equipped fluidized bed. The weight of the layered pellets was 140 g.

[0085] Pellets (corresponding to approx. 10 mg active substance) were analyzed using USP dissolution apparatus No. 2 (paddle) and operated at 100 rpm and 37°C. First the pellets were immersed n 0.1M HCl for 2 hours (pH 1.2), thereafter phosphate buffer components were added to obtain pH 6.8. The dissolution profile was registered as described in example 1, and is shown in Figure 3. The pellets were examined with respect to acid resistance. After exposure to 0.1 M HCl during two hours, 96 % of the active substance remained intact.

Example 4.

[0086] Single dose layered pellets, i.e. enteric coated pulsed single dose delayed release pellets comprising magnesium salt of omeprazole (pellet strength approx. 35 mg/g.).

Preparation of core material (spheres layered with drug).

[0087] A drug containing suspension was made according to the composition below;

Omeprazole Mg-salt	100 g
HPMC, 6 cps	15 g
Polysorbate 80	2 g
Purified water	323 g

[0088] HPMC was dissolved in the water during stirring with subsequent addition of Polysorbate 80 and the drug.

The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. After the coating the weight of the obtained product was 395 g.

Application of swelling layer

[0089] A (water free) suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

[0090] HPC-LF was dissolved in ethanol during stirring, then the talc and the swelling agent L-HPC was added. The suspension was sprayed onto 175 g of core material from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

Application of lag time controlling layer (semipermeable membrane).

[0091] 120 grams of the swelling layered pellets (the fraction 0.61 mm - 0.71 mm obtained by sieving) obtained above were coated with the suspension below;

Ethylcellulose, 10 cps	8 g
Talc	18 g
EtOH (99.5%)	810 g

[0092] The suspension was prepared by dissolving ethylcellulose in ethanol during stirring, then talc was added. The suspension was sprayed onto the pellets in a Wurster equipped fluidized bed. The weight of the obtained product was 137 g.

Application of enteric coating layer.

[0093] 120 grams of the pellets from the previous step above were coated with an enteric coating solution according to below;

HPMCP (HP-55)	33 g
Cetanol	2.4 g
Acetone	353 g
EtOH (99.5%)	151 g

[0094] The coating solution was prepared by dissolving HPMCP and cetanol in a mixture of the solvents during stirring. The coating solution was applied in a Wurster equipped fluidized bed. The weight of the layered pellets was 149 g.

[0095] The layered pellets were examined with respect to acid resistance in 0.1 M HCl. The acid resistance was 97 %.

Example 5.

[0096] Single dose layered tablets, i.e. enteric coated pulsed single dose delayed release tablets comprising magnesium salt of S-omeprazole (Tablet strength approx. 16 mg).

Granules

[0097] Granules for homogeonous tablet cores were made according to the following composition;

S-omeprazole Mg-salt	229 g

(continued)

Microcrystalline cellulose, Avicel pH 101	151 g
Microcrystalline cellulose, Avicel PH 102 sp. coarse grade	400 g
L-HPC	256 g
PVP-XL	302 g
Sodium laurylsulphate (SLS)	30 g
Water purified	1060 g

[0098] A granulating solution was prepared by dissolving the SLS in 460 g of purified water.

[0099] The powders above were mixed in a mixer after which the solution was added in an even stream. Thereafter approx. 600 g water was added during continued mixing, to give satisfactory consistency to the mass.

[0100] The mass was dried in a drying oven at 50°C over night.

Preparation of tablet cores

[0101] After milling through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, sodium chloride, and an additional amount of swellable substance, according to the following composition;

Granules for tablet core	400 g
Sodium chloride (passing 0.3mm)	80 g
Sodium stearyl fumarate (Pruv®)	8 g
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20 g

[0102] The mixing was performed to homogeneity in a Kenwood mixer.

[0103] The mixture was compressed to 6 mm in diameter tablets having an average weight of 126 mg, on a single punch tableting machine (Diaf).

Application of lag time controlling layer (semipermeable membrane).

[0104] The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until the average tablet weight was 134 mg.

Application of enteric coating layer

[0105] The tablets obtained in the previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	16 parts by weight
Cetanol	1 - " -
Acetone	151 - " -
Ethanol (95% w/v)	65 - " -
Sum:	233 parts

100 grams of the tablets were processed and the coating was continued until the average tablet weight was 148 mg.

[0106] Individual tablets were analyzed using USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets and operated at 100 rpm and 37°C. First the tablets were pre-exposed for 0.1 M HCl for two hours (pH 1.2), whereafter the dissolution medium was changed to phosphate buffer pH 6.8.

[0107] The dissolution profile obtained was registered as described in example 1, and can be seen in Figure 4.

Example 6.

[0108] Multiple dose layered tablets, i.e. enteric coated dual pulsed multiple release tablets. (tablet strength approx. 2 x 15 mg).

Granules

[0109] Granules for tablet cores were made according to the following composition;

S-omeprazole Mg-salt	229 g
Microcrystalline cellulose, Avicel PH 101	151 g
Microcrystalline cellulose, Avicel PH 102 sp. Coarse grade	400 g
L-HPC	256 g
PVP-XL	302 g
Sodium laurylsulphate (SLS)	30 g
Water purified	1060 g

[0110] A granulating solution was prepared by dissolving the SLS in 460 g of purified water.
[0111] The powders above were mixed in a mixer after which the solution was added in an even stream. Thereafter approx. 600 g water was added during continued mixing, to give satisfactory consistency to the mass.
[0112] The mass was dried in a drying oven at 50°C over night.

Preparation of tablet cores

[0113] After milling through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, sodium chloride, and an additional amount of swellable substance, according to the following composition;

Granules for homogenous tablet core	400
Sodium chloride (passing 0.3mm)	80
Sodium stearyl fumarate (Pruv®)	8
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20

[0114] The mixing was performed to homogeneity in a Kenwood mixer.
[0115] The mixture was compressed to 6 mm in diameter tablets having an average weight of 126 mg, on a single punch tableting machine (Diaf).

Application of lag time controlling layer (semipermeable membrane).

[0116] The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until average tablet weight was 134 mg.

Application of a drug comprising layer

[0117] The tablets obtained in previous step were coated in the same equipment as above with a coating suspension of the following composition;

S-omeprazole Mg-salt	20 parts by weight
Hydroxypropyl methylcellulose 6 cps	13 parts by weight
Ethanol 99%	128 parts by weight
Water purified	128 parts by weight
Sum:	289 parts.

99 grams of tablets were processed and the coating was continued until the average tablet weight was 162 mg.

Application of enteric coating layer

[0118] The tablets obtained in previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55)	16 parts by weight
Cetanol	1 - " -
Acetone	153 - " -
Ethanol (95% w/v)	65 - " -
Sum:	235 parts

119 grams of the tablets were processed and the coating was continued until the average tablet weight was 173 mg.

[0119] Individual tablets were analyzed using USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets and operated at 100 rpm and 37°C. First the tablets were pre-exposed for 0.1 M HCl for two hours, whereafter the dissolution medium was changed to phosphate buffer pH 6.8.

[0120] The dissolution profile obtained was registered as described in example 1, and can be seen in Figure 5. The acid resistance of the tablets were examined and the result was 98 %.

Example 7

[0121] Multiple dose capsule formulation comprising (2 x 20) mg of omeprazole in the form of enteric coated pellets, mixed with an enteric coated tablet with delayed release.

Suspension layering	
Magnesium omeprazole	5 kg
Sugar spheres cores (0.25-0.355 mm diam.)	10 kg
Hydroxypropyl methylcellulose	0.8 kg
Water purified	20 kg

Separating layer	
Drug containing cores (acc. to above)	14.6 kg
Hydroxypropyl cellulose	1.5 kg
Talc	2.5 kg
Magnesium Stearate	0.2 kg
Water purified	29 kg

Enteric coating	
Pellets (acc. to above)	9 kg
Methacrylic acid copolymer (30% suspension)	15 kg
Triethyl citrate	1.4 kg
Mono- and diglycerides (NF)	0.2 kg
Polysorbate 80	0.02 kg

(continued)

Enteric coating	
Water purified	9 kg

Over-coating	
Enteric coated pellets	9 kg
Hydroxypropyl methylcellulose	0.2 kg
Mg-Stearate	0.005 kg
Water purified	3.6 kg

[0122] Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert sugar sphere cores from a water suspension containing the dissolved binder.

[0123] The prepared core material was sub-coated in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate.

The enteric coating consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the sub-coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coated pellets were coated with hydroxypropyl methylcellulose/Mg-Stearate suspension. The over-coated pellets were classified by sieving, to pass 0.71 mm.

[0124] The product was analyzed and found to contain 209 mg/g Mg-omeprazole.

[0125] Single dose layered tablets, i.e. enteric coated delayed release tablets comprising magnesium salt of omeprazole. (Tablet strength approx. 16 mg.)

Granules

[0126] Granules for tablet cores were made according to the following composition (parts by weight);

Omeprazole Mg-salt	229 g
Microcrystalline cellulose, Avicel PH 101	145 g
Microcrystalline cellulose, Avicel PH 102 sp. coarse grade	400 g
L-HPC	251 g
PVP-XL	302 g
Hydroxy methylcellulose 6 cps	I 1 g
Sodium laurylsulphate (SLS)	30 g
Water purified	960 g

[0127] A granulating solution was prepared by dissolving the SLS in 460 g of purified water.

[0128] The powders above were mixed in a mixer after which the solution was added in an even stream. Thereafter approx. 500 g water was added during continued mixing, to give satisfactory consistency to the mass.

[0129] The mass was dried in a drying oven at 50°C over night.

Preparation of tablet cores

[0130] After milling through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, sodium chloride and an additional amount of swellable substance, according to the following composition;

Granules for tablet core	400 g
Sodium chloride (passing 0.3mm)	80 g
Sodium stearyl fumarate (Pruv®)	8 g
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20 g

[0131] The mixing was performed to homogeneity in a Kenwood mixer.

[0132] The mixture was compressed to 6 mm in diameter tablets having an average weight of 126 mg, on a single

punch tableting machine (Diaf).

Application of lag time regulating layer (semipermeable membrane).

[0133] The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until the average tablet weight was 134 mg.

Application of enteric coating layer

[0134] The tablets obtained in previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	16 parts by weight
Cetanol	1 - " -
Acetone	151 - " -
Ethanol (95% w/v)	65 - " -
Sum:	233 parts

100 grams of the tablets were processed and the coating was continued until the average tablet weight was 148 mg.

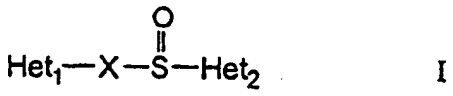
Filling of capsule

[0135] 0.10 g of the pellets prepared above and one of the layered tablets obtained above were filled in a hard gelatine capsule size 1.

[0136] The best mode to practice the invention is according to the description given in Example 6.

Claims

1. An enteric coated pharmaceutical dosage form giving a discontinuous release of a H^+, K^+-ATPase inhibitor, **characterized in that** the release of the H^+K^+-ATPase inhibitor is in the form of at least two consecutive pulses separated in time by from 0.5 and up to 12 hours, and at least one fraction of the dosage form has a pulsed delayed release and another fraction has instant release, and the H^+,K^+-ATPase inhibitor is a compound with the formula I, an alkaline salt of compound I, a single enantiomer of compound I or an alkaline salt of the single enantiomer of compound I



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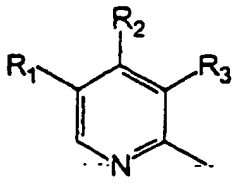

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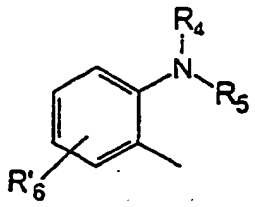

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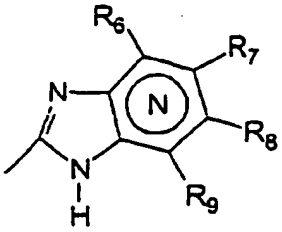

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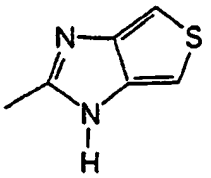

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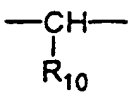

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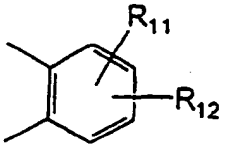


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and arylalkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolinyl, and trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

2. A dosage form according to claim 1 **characterized in that** the H^+,K^+-ATPase inhibitor is omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole or an alkaline salt of the (-)-enantiomer of omeprazole.

3. A dosage form according to claim 2, **characterized in that** the alkaline salt is a magnesium salt.

4. A dosage form according to claim 1 **characterized in that** the H^+,K^+-ATPase inhibitor is lansoprazole, alkaline salts thereof, a single enantiomer thereof or an alkaline salt thereof.

5. A dosage form according to any of claims 1-4 **characterized in that** it comprises

a) a core material comprising one portion of the H^+,K^+-ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients,

b) the following sequence of layers, covering the core material

b1) a lag time controlling layer,
b2) at least an additional layer comprising the second portion of the H^+,K^+-ATPase inhibitor, and
b3) an enteric coating layer.

6. A dosage form according to any of claims 1-4 **characterized in that** it comprises

a) a core material comprising one portion of the H^+,K^+-ATPase inhibitor and optionally pharmaceutically acceptable excipients,

b) the following sequence of layers, covering the core material

b1) a swelling layer comprising a water swellable substance,
b2) a lag time controlling layer,
b3) at least an additional layer comprising the second portion the H^+,K^+-ATPase inhibitor, and
b4) an entenc coating layer.

7. A dosage form according to any of claims 1-4 **characterized in that** it comprises at least two populations of pellets or tablets or any combinations thereof, **characterized in that** it comprises

a) the first population which has a core material comprising one portion of the H^+, K^+-ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients, and wherein the core material is covered by a lag time controlling layer and an enteric coating layer, and

b) the second population of pellets or tablets which has a core material comprising the second portion of the H^+,K^+-ATPase inhibitor and optionally pharmaceutically acceptable excipients, and the second core material is covered by an enteric coating layer.

8. A dosage form according to any of claims 1-4 **characterized in that** it comprises at least two populations of pellets or tablets or any combinations thereof, **characterized in that**

a) the first population comprises a core material comprising one portion of the H^+,K^+-ATPase inhibitor and optionally pharmaceutically acceptable excipients, wherein the core material is covered by a swelling layer comprising a water swellable substance, a lag time controlling layer and an enteric coating layer, and

b) the second population of pellets or tablets has a core material comprising a second portion of the H^+, K^+-ATPase inhibitor and optionally pharmaceutically acceptable excipients, and the second core material is covered by an enteric coating layer.

9. A dosage form according to any of claims 7 and 8 **characterized in that** one or more additional layer comprising an additional portion of the H^+,K^+-ATPase inhibitor is applied under the enteric coating layer of the first population a).

10. A dosage form according to any of the claims 1-9 **characterized in that** the two portions of the H^+,K^+-ATPase inhibitor are released as two discret pulses separated in time by from 0.5 and up to 4 hours.

11. A dosage form according to any of claims 5-10, **characterized in that** the H^+,K^+-ATPase inhibitor further comprises an admixture of an alkaline additive.

12. A dosage form according to any of claims 5-10 **characterized in that** the water swellable substance is selected form the group of low-substituted hydroxypropyl cellulose, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose and sodium starch glycolate.

13. A dosage form according to any of claims 5 - 10 **characterized in that** the lag time controlling layer comprises a water resistant membrane which is semipermeable for an aqueous solution, such as intestinal fluid.

14. A dosage form according to claim 13, **characterized in that** the lag time controlling layer is a disrupting semipermeable membrane.

15. A dosage form according to claim 13 **characterized in that** the weight of the lag time controlling layer constitutes from 0.5 to 25 % counted on the weight of the core material including water swelling substances or a swelling layer.

16. A dosage form according to any of claims 7-10 **characterized in that** the two or more populations of pellets or tablets or any combinations thereof are filled in a capsule.

17. A dosage form according to any of claims 7 - 10 **characterized in that** two or more populations of pellets with different release pattern of the H^+,K^+-ATPase inhibitor are mixed together with pharmaceutically acceptable excipients and compressed into a multiple unit tableted dosage form.

18. A dosage form according to any of claims 5 - 10 **characterized in that** a separating layer is present beneath the enteric coating layer.

19. A dosage form according to any of claims 5 - 10 **characterized in that** the core material comprises a seed layered with the H^+,K^+-ATPase inhibitor.

20. A layered pellet or tablet for the dosage form defined in any of claims 1-6 **characterized in that** the pellet or tablet comprises a core material comprising one portion of the H^+,K^+-ATPase inhibitor, a water swellable substance and optionally pharmaceutically acceptable excipients, wherein the core material is covered by a lag time controlling layer and an enteric coating layer, optionally at least one an additional layer comprising an additional portion of the H^+,K^+-ATPase inhibitor is applied under the enteric coating layer.

21. A layered pellet or tablet for the dosage form defined in any of claims 1-6 **characterized in that** the pellet or tablet comprises a core material comprising one portion of the H^+, K^+-ATPase inhibitor and optionally pharmaceutically acceptable excipients, the core material is covered by a swelling layer comprising water swellable substances, a lag time controlling layer and an enteric coating layer, optionally at least one an additional layer comprising an additional portion of the H^+,K^+-ATPase inhibitor is applied under the enteric coating layer.

22. A process for the preparation of an enteric coated dosage form comprising a H^+,K^+-ATPase inhibitor in which dosage form the inhibitor compound is present in at least two portions giving a release of the H^+,K^+-ATPase inhibitor in at least two separate pulses, which process comprises the following steps:

a) a core material is shaped comprising one portion of the H^+,K^+-ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients,

b) the core material is layered with the following layers:

b1) a lag time controlling layer,
b2) a layer comprising the second portion of the H^+,K^+-ATPase inhibitor, and
b3) the enteric coating layer.

23. A process for the preparation of an enteric coated dosage form comprising a H^+,K^+-ATPase inhibitor in which dosage form the inhibitor compound is present in at least two portions giving a release of the H^+,K^+-ATPase inhibitor in at least two separate pulses, which process comprises the follow steps:

a) a core material is shaped comprising one portion of the H^+,K^+-ATPase inhibitor optionally mixed with pharmaceutically acceptable excipients,

b) the core material is layered with the following layers:

b1) a swelling layer comprising a water swellable substance,
b2) a lag time controlling layer,
b3) a layer comprising the second portion of the H^+,K^+-ATPase inhibitor, and
b4) the enteric coating layer.

24. A process for the preparation of a dosage form according to any of claims 22 or 23, wherein an additional layer comprising the H^+,K^+-ATPase inhibitor is applied before the enteric coating layer is applied.

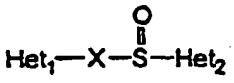
25. An enteric coated pharmaceutical dosage form according to any of claims 1-19 for use in medicine.

26. Use of an enteric coated pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

27. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

Patentansprüche

1. Magensaftresistent beschichtete pharmazeutische Dosisform mit diskontinuierlicher Freigabe eines H^+,K^+-ATPase-Inhibitors, **dadurch gekennzeichnet, daß** die Freigabe des H^+,K^+-ATPase-Inhibitors in Form von mindestens zwei aufeinanderfolgenden Pulsen mit einem zeitlichen Abstand von 0,5 bis 12 Stunden erfolgt, mindestens ein Teil der Dosisform eine gepulste verzögerte Freigabe und ein anderer Teil sofortige Freigabe aufweist und es sich bei dem H^+,K^+-ATPase-Inhibitor um eine Verbindung der Formel I, ein alkalisches Salz der Verbindung I, ein Einzelenantiomer der Verbindung I oder ein alkalisches Salz des Einzelenantiomers der Verbindung I



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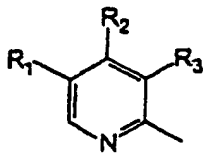

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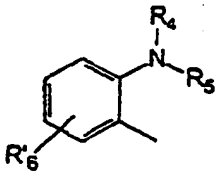

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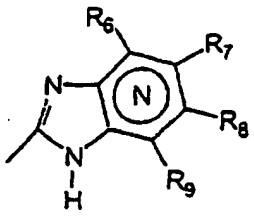

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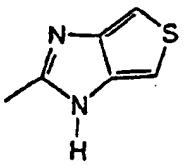

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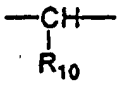

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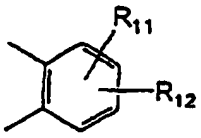

worin

N in der Bezimidazolgruppierung bedeutet, daß eines der durch R_6-R_9 substituierten Ringkohlenstoffatome gegebenenfalls durch ein Stickstoffatom ohne Substituenten ersetzt sein kann;

R_1, R_2 und R_3 gleich oder verschieden sind und aus der Gruppe bestehend aus Wasserstoff, Alkyl, durch Fluor substituiertes Alkoxy, Alkylthio, Alkoxyalkoxy, Dialkylamino, Piperidino, Morpholino, Halogen, Phenyl und Phenylalkoxy ausgewählt sind;

R_4 und R_5 gleich oder verschieden sind und aus der Gruppe bestehend aus Wasserstoff, Alkyl und Aralkyl ausgewählt sind;

R_6' für Wasserstoff, Halogen, Trifluormethyl, Alkyl oder Alkoxy steht;

R_6-R_9 gleich oder verschieden sind und aus der Gruppe bestehend aus Wasserstoff, Alkyl, Alkoxy, Halogen, Halogenalkoxy, Alkylcarbonyl, Alkoxycarbonyl, Oxazolinyl und Trifluoralkyl ausgewählt sind oder benachbarte Gruppen R_6-R_9 gegebenenfalls weiter substituierte Ringstrukturen bilden;

R_{10} für Wasserstoff steht oder gemeinsam mit R_3 eine Alkylenkette bildet und

R_{11} und R_{12} gleich oder verschieden sind und aus der Gruppe bestehend aus Wasserstoff, Halogen oder Alkyl ausgewählt sind;

handelt.

2. Dosisform nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem H^+,K^+-ATPase-Inhibitor um Omeprazol, ein alkalisches Salz von Omeprazol, das (-)-Enantiomer von Omeprazol oder ein alkalisches Salz des (-)-Enantiomers von Omeprazol handelt.

3. Dosisform nach Anspruch 2, **dadurch gekennzeichnet, daß** es sich bei dem alkalischen Salz um ein Magnesiumsalz handelt.

4. Dosisform nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem H^+,K^+-ATPase-Inhibitor um Lansoprazol, alkalische Salze davon, ein Einzelenantiomer davon oder ein alkalisches Salz davon handelt.

5. Dosisform nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** sie

a) ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors, eine wasserquellbare Substanz und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält,

b) die folgende Abfolge von Schichten über dem Kernmaterial

b1) eine die Verzögerungszeit regulierende Schicht,
b2) mindestens eine zusätzliche Schicht, die die zweite Portion des H^+,K^+-ATPase-Inhibitors enthält, und
b3) eine magensaftresistente Schicht

enthält.

6. Dosisform nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** sie

a) ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält,

b) die folgende Abfolge von Schichten über dem Kernmaterial

b1) eine Quellschicht, die eine wasserquellbare Substanz enthält,
b2) eine die Verzögerungszeit regulierende Schicht,
b3) mindestens eine zusätzliche Schicht, die die zweite Portion des H^+,K^+-ATPase-Inhibitors enthält, und
b4) eine magensaftresistente Schicht

enthält.

7. Dosisform nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** sie mindestens zwei Populationen von Pellets oder Tabletten oder beliebige Kombinationen davon enthält, **dadurch gekennzeichnet, daß** sie

a) die erste Population, die ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält und von einer die Verzögerungszeit regulierenden Schicht und einer magensaftresistenten Schicht bedeckt ist, aufweist, und

b) die zweite Population von Pellets oder Tabletten, die ein Kernmaterial, das die zweite Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält- und von einer magensaftresistenten Schicht bedeckt ist, aufweist,

enthält.

8. Dosisform nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** sie mindestens zwei Populationen von Pellets oder Tabletten oder beliebige Kombinationen davon enthält, **dadurch gekennzeichnet, daß**

a) die erste Population ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält und von einer eine wasserquellbare Substanz enthaltenden Quellschicht, einer die Verzögerungszeit regulierenden Schicht und einer magensaftresistenten Schicht bedeckt ist, aufweist, und

b) die zweite Population von Pellets oder Tabletten ein Kernmaterial, das eine zweite Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält und von einer magensaftresistenten Schicht bedeckt ist, aufweist.

9. Dosisform nach einem der Ansprüche 7 und 8, **dadurch gekennzeichnet, daß** unter der magensaftresistenten Schicht der ersten Population a) eine oder mehrere zusätzliche Schichten, die eine zusätzliche Portion des H^+,K^+-ATPase-Inhibitors enthalten, aufgebracht sind.

10. Dosisform nach einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, daß** die beiden Portionen des H^+,K^+-ATPase-Inhibitors in Form von zwei diskreten Pulsen mit einem zeitlichen Abstand von 0,5 bis 4 Stunden freigegeben werden.

11. Dosisform nach einem der Ansprüche 5 bis 10, **dadurch gekennzeichnet, daß** der H^+,K^+-ATPase-Inhibitor außerdem eine Beimischung eines alkalischen Additivs enthält.

12. Dosisform nach einem der Ansprüche 5 bis 10, **dadurch gekennzeichnet, daß** die wasserquellbare Substanz aus der Gruppe niedersubstituierte Hydroxypropylcellulose, vernetztes Polyvinylpyrrolidon, vernetzte Natriumcarboxymethylcellulose und Natriumstärkeglykolat stammt.

13. Dosisform nach einem der Ansprüche 5 bis 10, **dadurch gekennzeichnet, daß** es sich bei der die Verzögerungszeit regulierenden Schicht um eine wasserbeständige Membran handelt, die für eine wäßrige Lösung wie Darmsaft semipermeabel ist.

14. Dosisform nach Anspruch 13, **dadurch gekennzeichnet, daß** es sich bei der die Verzögerungszeit regulierenden Schicht um eine zerreißende semipermeable Membran handelt.

15. Dosisform nach Anspruch 13, **dadurch gekennzeichnet, daß** das Gewicht der die Verzögerungszeit regulierenden Schicht sich auf 0,5 bis 25%, bezogen auf das Gewicht des Kernmaterials einschließlich wasserquellbarer Substanzen oder einer Quellschicht, beläuft.

16. Dosisform nach einem der Ansprüche 7 bis 10, **dadurch gekennzeichnet, daß** die zwei oder mehr Populationen von Pellets oder Tabletten oder beliebige Kombinationen davon in eine Kapsel abgefüllt sind.

17. Dosisform nach einem der Ansprüche 7 bis 10, **dadurch gekennzeichnet, daß** zwei oder mehr Populationen von Pellets mit verschiedenem Freigabemuster für den H^+,K^+-ATPase-Inhibitor mit pharmazeutisch unbedenklichen Trägerstoffen vermischt und zu einer tablettierten Multiple-Unit-Dosisform verpreßt sind.

18. Dosisform nach einem der Ansprüche 5 bis 10, **dadurch gekennzeichnet, daß** unter der magensaftresistenten Schicht eine Trennschicht vorhanden ist.

19. Dosisform nach einem der Ansprüche 5 bis 10, **dadurch gekennzeichnet, daß** das Kernmaterial einen mit dem H^+,K^+-ATPase-Inhibitor beschichteten Keim enthält.

20. Beschichtetes Pellet oder beschichtete Tablette für die Dosisform nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, daß** das Pellet oder die Tablette ein Kernmaterial enthält, das eine Portion des H^+,K^+-ATPase-Inhibitors, eine wasserquellbare Substanz und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält und von einer die Verzögerungszeit regulierenden Schicht und einer magensaftresistenten Schicht bedeckt ist, wobei unter der magensaftresistenten Schicht gegebenenfalls mindestens eine zusätzliche Schicht, die eine zusätzliche Portion des H^+,K^+-ATPase-Inhibitors enthält, aufgebracht ist.

21. Beschichtetes Pellet oder beschichtete Tablette für die Dosisform nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, daß** das Pellet oder die Tablette ein Kernmaterial enthält, das eine Portion des H^+,K^+-ATPase-Inhibitors und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält und von einer wasserquellbare Substanzen enthaltenden Quellschicht, einer die Verzögerungszeit regulierenden Schicht und einer magensaftresistenten Schicht bedeckt ist, wobei unter der magensaftresistenten Schicht gegebenenfalls mindestens eine zusätzliche Schicht, die eine zusätzliche Portion des H^+,K^+-ATPase-Inhibitors enthält, aufgebracht ist.

22. Verfahren zur Herstellung einer magensaftresistent beschichteten Dosisform, die einen H^+,K^+-ATPase-Inhibitor enthält, und bei der die Inhibitorverbindung in mindestens zwei Portionen vorliegt, was eine Freigabe des H^+,K^+-ATPase-Inhibitors in mindestens zwei separaten Pulsen ergibt, bei dem man:

a) ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors, eine wasserquellbare Substanz und gegebenenfalls pharmazeutisch unbedenkliche Trägerstoffe enthält, formt,

b) das Kernmaterial mit den folgenden Schichten beschichtet:

b1) einer die Verzögerungszeit regulierenden Schicht,
b2) mindestens einer Schicht, die die zweite Portion des H^+,K^+-ATPase-Inhibitors enthält, und
b3) der magensaftresistenten Schicht.

23. Verfahren zur Herstellung einer magensaftresistent beschichteten Dosisform, die einen H^+,K^+-ATPase-Inhibitor enthält, und bei der die Inhibitorverbindung in mindestens zwei Portionen vorliegt, was eine Freigabe des H^+,K^+-ATPase-Inhibitors in mindestens zwei separaten Pulsen ergibt, bei dem man:

    a) ein Kernmaterial, das eine Portion des H^+,K^+-ATPase-Inhibitors, gegebenenfalls in Abmischung mit pharmazeutisch unbedenklichen Trägerstoffen, enthält, formt,

    b) das Kernmaterial mit den folgenden Schichten beschichtet:

        b1) einer Quellschicht, die eine wasserquellbare Substanz enthält,
        b2) einer die Verzögerungszeit regulierenden Schicht,
        b3) einer Schicht, die die zweite Portion des H^+,K^+-ATPase-Inhibitors enthält, und
        b4) der magensaftresistenten Schicht.

24. Verfahren zur Herstellung einer Dosisform nach Anspruch 22 oder 23, bei dem man vor dem Aufbringen der magensaftresistenten Schicht eine zusätzliche Schicht, die den H^+,K^+-ATPase-Inhibitor enthält, aufbringt.

25. Magensaftresistent beschichtete pharmazeutische Dosisform nach einem der Ansprüche 1 bis 19 zur Verwendung in der Medizin.

26. Verwendung einer magensaftresistent beschichteten pharmazeutischen Dosisform nach einem der Ansprüche 1 bis 19 bei der Herstellung eines Arzneimittels mit verbesserter Hemmung der Magensäuresekretion.

27. Verwendung einer oralen pharmazeutischen Dosisform nach einem der Ansprüche 1 bis 19 bei der Herstellung eines Arzneimittels mit verbesserter therapeutischer Wirkung bei der Behandlung von gastrointestinalen Störungen, die mit übermäßiger Säuresekretion einhergehen.

Revendications

1. Forme galénique à enrobage entérique procurant une libération discontinue d'un inhibiteur de H^+,K^+-ATPase, **caractérisée en ce que** la libération de l'inhibiteur de H^+,K^+-ATPase est sous la forme d'au moins deux impulsions consécutives séparées dans le temps d'une période allant de 0,5 jusqu'à 12 heures, et au moins une fraction de la forme galénique présente une libération retardée pulsée et une autre fraction présente une libération instantanée, et l'inhibiteur de H^+,K^+-ATPase est un composé de formule I, un sel alcalin du composé I, un énantiomère unique du composé I ou un sel alcalin de l'énantiomère unique du composé I

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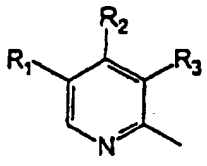

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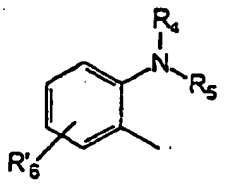

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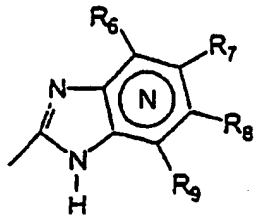

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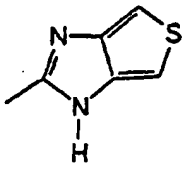

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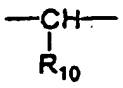

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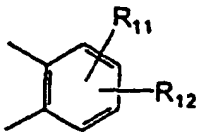


où

N dans le fragment benzimidazole signifie que l'un des atomes de carbone cyclique substitués par R_6-R_9 peut être éventuellement remplacé par un atome d'azote sans aucun substituant ;

R_1, R_2 et R_3 sont identiques ou différents et choisis parmi un hydrogène, un alkyle, un alcoxy éventuellement substitué par un fluor, un alkylthio, un alcoxyalcoxy, un dialkylamino, un pipéridino, un morpholino, un halogène, un phényle et un phénylalcoxy ;

R_4 et R_5 sont identiques ou différents et choisis parmi un hydrogène, un alkyle et un arylalkyle ;

$R^{6'}$ est un hydrogène, un halogène, un trifluorométhyle, un alkyle ou un alcoxy ;

R_6-R_9 sont identiques ou différents et choisis parmi un hydrogène, un alkyle, un alcoxy, un halogène, un halogénoalcoxy, un alkylcarbonyle, un alcoxycarbonyle, un oxazolinyle et un trifluoroalkyle, ou des groupes adjacents R_6-R_9 forment des structures cycliques qui peuvent être davantage substituées ;

R_{10} est un hydrogène ou forme une chaîne alkylène conjointement avec R_3 et

R_{11} et R_{12} sont identiques ou différents et choisis parmi un hydrogène, un halogène ou un alkyle.

2. Forme galénique selon la revendication 1, **caractérisée en ce que** l'inhibiteur de H^+,K^+-ATPase est l'oméprazole, un sel alcalin de l'oméprazole, l'énantiomère (-) de l'oméprazole ou un sel alcalin de l'énantiomère (-) de l'oméprazole.

3. Forme galénique selon la revendication 2, **caractérisée en ce que** le sel alcalin est un sel de magnésium.

4. Forme galénique selon la revendication 1, **caractérisée en ce que** l'inhibiteur de H^+,K^+-ATPase est le lansoprazole, des sels alcalins de celui-ci, un énantiomère unique de celui-ci ou un sel alcalin de celui-ci.

5. Forme galénique selon l'une quelconque des revendications 1 à 4, **caractérisée en ce qu'**elle comprend

a) une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase, une substance gonflable dans l'eau et éventuellement des excipients pharmaceutiquement acceptables,

b) la séquence suivante de couches, recouvrant la matière de coeur

b1) une couche régulant le temps de latence,
b2) au moins une couche supplémentaire comprenant la deuxième portion de l'inhibiteur de H^+,K^+-ATPase, et
b3) une couche d'enrobage entérique.

6. Forme galénique selon l'une quelconque des revendications 1 à 4, **caractérisée en ce qu'**elle comprend

a) une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase et éventuellement des excipients pharmaceutiquement acceptables,

b) la séquence suivante de couches, recouvrant la matière de coeur

b1) une couche gonflante comprenant une substance gonflable dans l'eau,
b2) une couche régulant le temps de latence,
b3) au moins une couche supplémentaire comprenant la deuxième portion de l'inhibiteur de H^+,K^+-ATPase, et
b4) une couche d'enrobage entérique.

7. Forme galénique selon l'une quelconque des revendications 1 à 4, **caractérisée en ce qu'**elle comprend au moins deux populations de pastilles ou de comprimés ou leurs combinaisons quelconques, **caractérisée en ce qu'**elle comprend

a) la première population qui présente une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase, une substance gonflable dans l'eau et éventuellement des excipients pharmaceutiquement acceptables, et où la matière de coeur est recouverte d'une couche régulant le temps de latence et d'une couche d'enrobage entérique, et
b) la deuxième population de pastilles ou de comprimés, qui présente une matière de coeur comprenant la deuxième portion de l'inhibiteur de H^+,K^+-ATPase et éventuellement des excipients pharmaceutiquement acceptables, et la deuxième matière de coeur est recouverte d'une couche d'enrobage entérique.

8. Forme galénique selon l'une quelconque des revendications 1 à 4, **caractérisée en ce qu'**elle comprend au moins deux populations de pastilles ou de comprimés ou leurs combinaisons quelconques, **caractérisée en ce que**

a) la première population comprend une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase et éventuellement des excipients pharmaceutiquement acceptables, où la matière de coeur est recouverte d'une couche gonflante comprenant une substance gonflable dans l'eau, une couche régulant le temps de latence et une couche d'enrobage entérique, et

b) la deuxième population de pastilles ou de comprimés présente une matière de coeur comprenant une deuxième portion de l'inhibiteur de H^+,K^+-ATPase et éventuellement des excipients pharmaceutiquement acceptables, et la deuxième matière de coeur est recouverte d'une couche d'enrobage entérique.

9. Forme galénique selon l'une quelconque des revendications 7 et 8, **caractérisée en ce qu'**une ou plusieurs couches supplémentaires comprenant une portion supplémentaire de l'inhibiteur de H^+,K^+-ATPase sont appliquées sous la couche d'enrobage entérique de la première population a).

10. Forme galénique selon l'une quelconque des revendications 1 à 9, **caractérisée en ce que** les deux portions de l'inhibiteur de H^+,K^+-ATPase sont libérées sous forme de deux impulsions discrètes séparées dans le temps d'une période allant de 0,5 jusqu'à 4 heures.

11. Forme galénique selon l'une quelconque des revendications 5 à 10, **caractérisée en ce que** l'inhibiteur de H^+, K^+-ATPase comprend en outre un mélange d'un additif alcalin.

12. Forme galénique selon l'une quelconque des revendications 5 à 10, **caractérisée en ce que** la substance gonflable dans l'eau est choisie parmi le groupe constitué de l'hydroxypropylcellulose à faible degré de substitution, de la polyvinylpyrrolidone réticulée, de la carboxyméthylcellulose sodique réticulée et du glycolate d'amidon sodique.

13. Forme galénique selon l'une quelconque des revendications 5 à 10, **caractérisée en ce que** la couche régulant

le temps de latence comprend une membrane résistant à l'eau qui est semi-perméable vis-à-vis d'une solution aqueuse, telle que le fluide intestinal.

14. Forme galénique selon la revendication 13, **caractérisée en ce que** la couche régulant le temps de latence est une membrane semi-perméable perturbatrice.

15. Forme galénique selon la revendication 13, **caractérisée en ce que** le poids de la couche régulant le temps de latence constitue de 0,5 à 25 %, par rapport au poids de la matière de coeur, y compris les substances gonflant dans l'eau ou une couche gonflante.

16. Forme galénique selon l'une quelconque des revendications 7 à 10, **caractérisée en ce que** les deux populations ou plus de pastilles ou de comprimés ou leurs combinaisons quelconques sont chargées dans une capsule.

17. Forme galénique selon l'une quelconque des revendications 7 à 10, **caractérisée en ce que** deux populations ou plus de pastilles avec un modèle de libération différent de l'inhibiteur de H^+,K^+-ATPase sont mélangées conjointement avec des excipients pharmaceutiquement acceptables et comprimées en une forme galénique en comprimé à unités multiples.

18. Forme galénique selon l'une quelconque des revendications 5 à 10, **caractérisée en ce qu'**une couche de séparation est présente en dessous de la couche d'enrobage entérique.

19. Forme galénique selon l'une quelconque des revendications 5 à 10, **caractérisée en ce que** la matière de coeur comprend une graine stratifiée avec l'inhibiteur de H^+,K^+-ATPase.

20. Pastille ou comprimé stratifié pour la forme galénique définie dans l'une quelconque des revendications 1 à 6, **caractérisé en ce que** la pastille ou le comprimé comprend une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase, une substance gonflable dans l'eau et éventuellement des excipients pharmaceutiquement acceptables, où la matière de coeur est recouverte d'une couche régulant le temps de latence et d'une couche d'enrobage entérique, éventuellement au moins une couche supplémentaire comprenant une portion supplémentaire de l'inhibiteur de H+,K+-ATPase est appliquée sous la couche d'enrobage entérique.

21. Pastille ou comprimé stratifié pour la forme galénique définie dans l'une quelconque des revendications 1 à 6, **caractérisé en ce que** la pastille ou le comprimé comprend une matière de coeur comprenant une portion de l'inhibiteur de H^+,K^+-ATPase, et éventuellement des excipients pharmaceutiquement acceptables, la matière de coeur est recouverte d'une couche gonflante comprenant des substances gonflables dans l'eau, d'une couche régulant le temps de latence et d'une couche d'enrobage entérique, éventuellement au moins une couche supplémentaire comprenant une portion supplémentaire de l'inhibiteur de H^+,K^+-ATPase est appliquée sous la couche d'enrobage entérique.

22. Procédé de préparation d'une forme galénique à enrobage entérique comprenant un inhibiteur de H^+,K^+-ATPase, dans laquelle forme galénique le composé inhibiteur est présent dans au moins deux portions procurant une libération de l'inhibiteur de H^+,K^+-ATPase en au moins deux impulsions séparées, lequel procédé comprend les étapes suivantes :

a) une matière de coeur est mise en forme, comprenant une portion de l'inhibiteur de H^+,K^+-ATPase, une substance gonflable dans l'eau et éventuellement des excipients pharmaceutiquement acceptables,

b) la matière de coeur est stratifiée avec les couches suivantes :

b1) une couche régulant le temps de latence,
b2) une couche comprenant la deuxième portion de l'inhibiteur de H^+,K^+-ATPase, et
b3) la couche d'enrobage entérique.

23. Procédé de préparation d'une forme galénique à enrobage entérique comprenant un inhibiteur de H^+,K^+-ATPase, dans laquelle forme galénique le composé inhibiteur est présent dans au moins deux portions procurant une libération de l'inhibiteur de H^+,K^+-ATPase en au moins deux impulsions séparées, lequel procédé comprend les étapes suivantes :

a) une matière de coeur est mise en forme, comprenant une portion de l'inhibiteur de H^+,K^+-ATPase éventuellement mélangée avec des excipients pharmaceutiquement acceptables,

b) la matière de coeur est stratifiée avec les couches suivantes :

b1) une couche gonflante comprenant une substance gonflable dans l'eau,
b2) une couche régulant le temps de latence,
b3) une couche comprenant la deuxième portion de l'inhibiteur de H^+,K^+-ATPase, et
b4) la couche d'enrobage entérique.

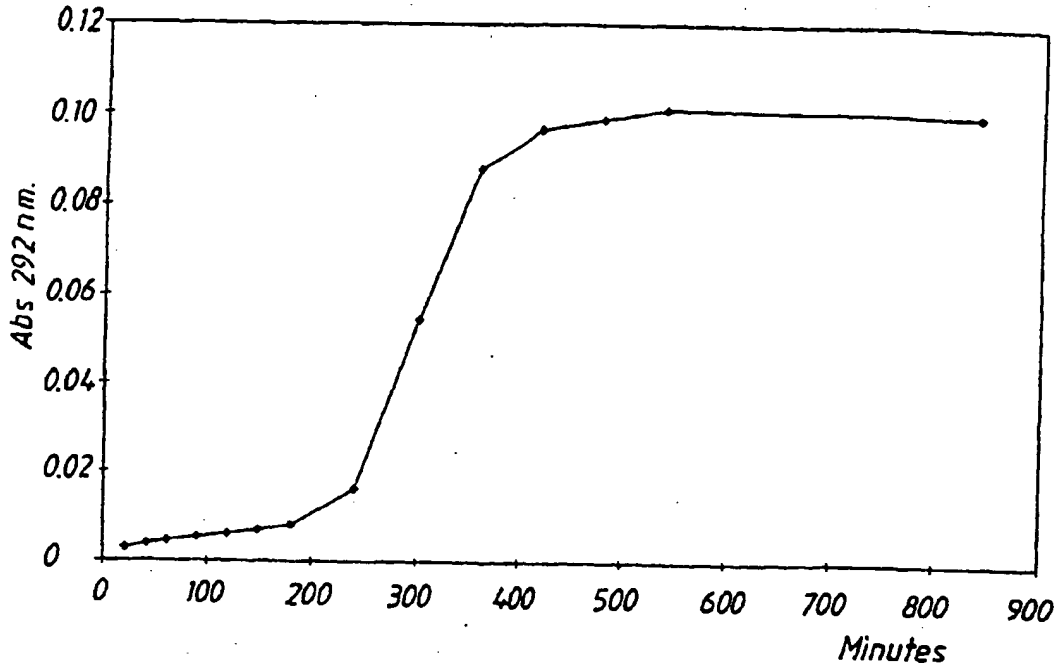
24. Procédé de préparation d'une forme galénique selon l'une quelconque des revendications 22 ou 23, dans lequel une couche supplémentaire comprenant l'inhibiteur de H^+,K^+-ATPase est appliquée avant d'appliquer la couche d'enrobage entérique.

25. Forme galénique à enrobage entérique selon l'une quelconque des revendications 1 à 19, destinée à être utilisée en médecine.

26. Utilisation d'une forme galénique à enrobage entérique selon l'une quelconque des revendications 1 à 19, pour la fabrication d'un médicament présentant une inhibition améliorée de la sécrétion d'acide gastrique.

27. Utilisation d'une forme galénique orale telle que définie dans l'une quelconque des revendications 1 à 19, pour la fabrication d'un médicament présentant un effet thérapeutique amélioré dans le traitement de troubles gastro-intestinaux associés à un excès de sécrétion d'acide.

Fig. 1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800
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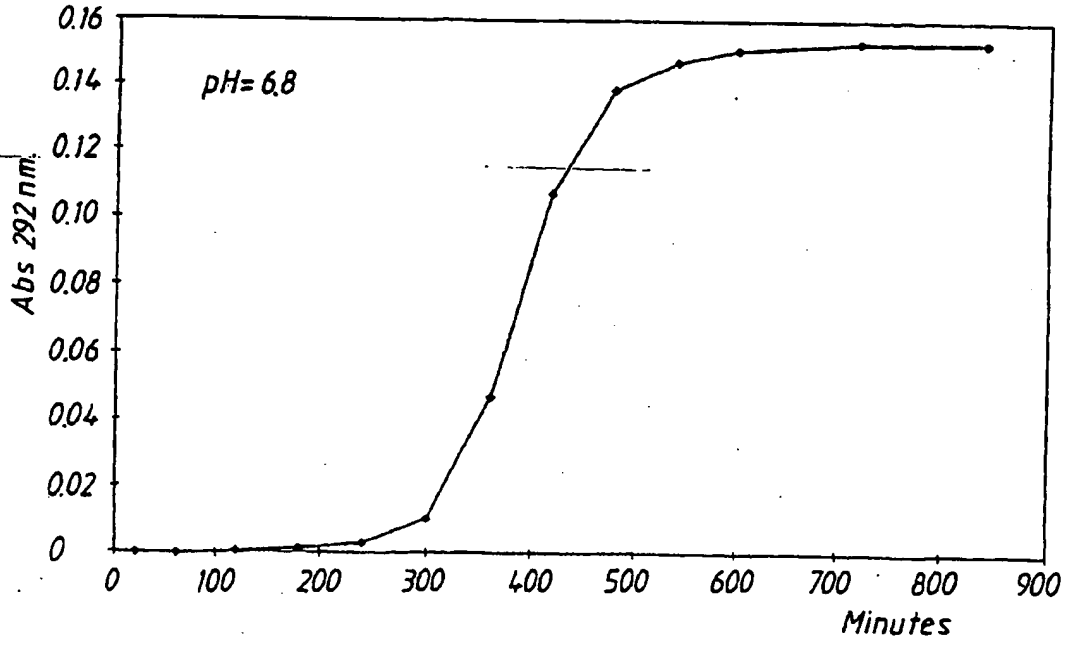
Minutes

Fig. 2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500
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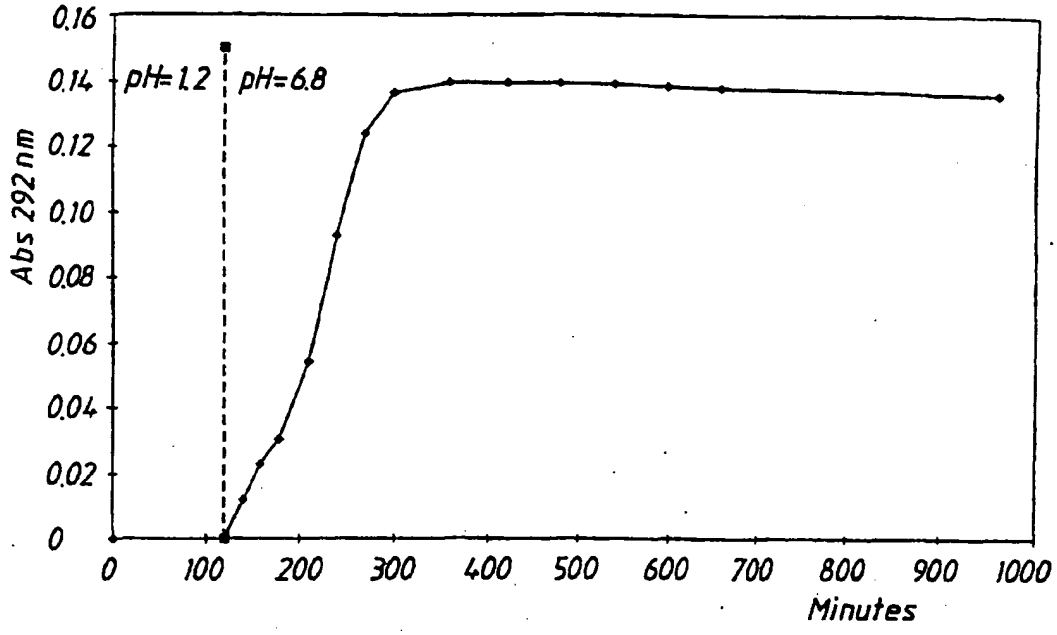
Minutes

Fig.3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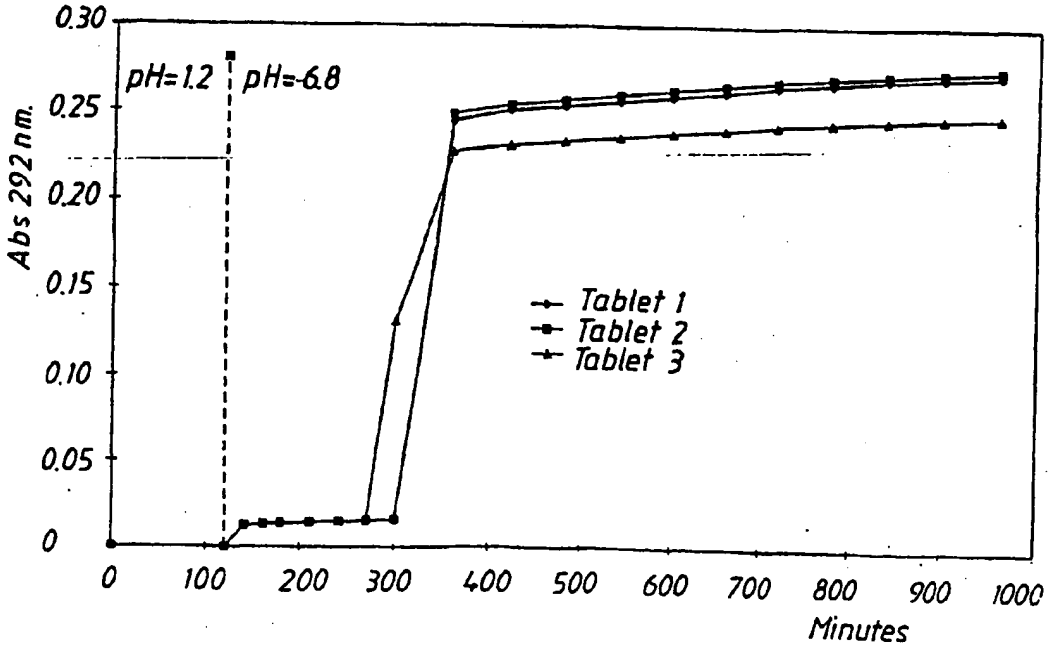
Minutes

Fig.4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Tablet 2
Tablet 3
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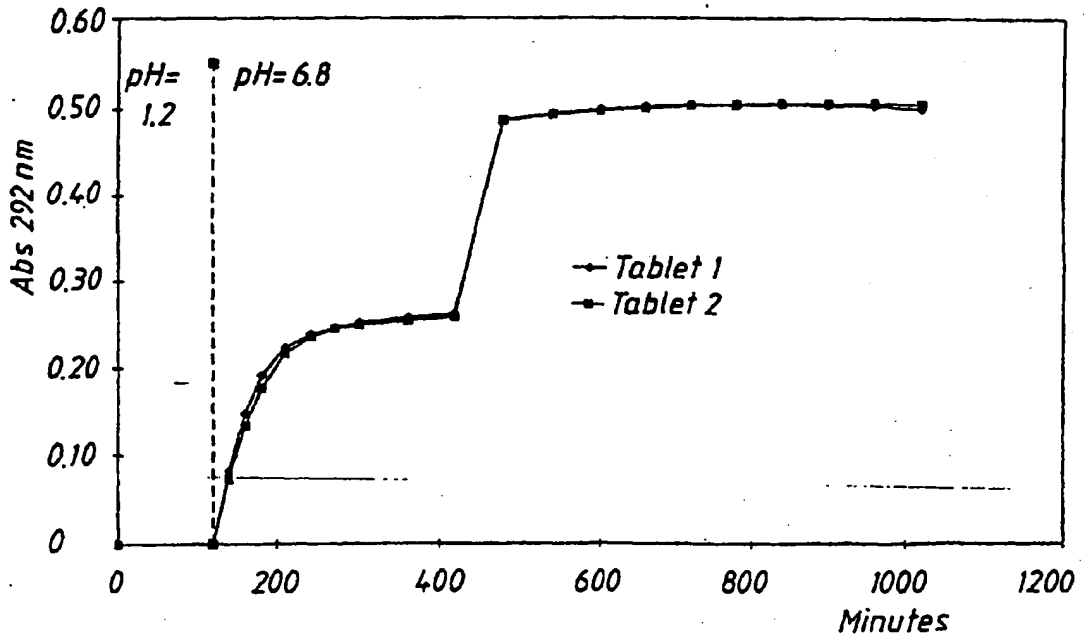
600
700
800
900
1000
Minutes

Fig.5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